87939

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Kanak M. George Examiner #: 77560 Date: 3/3/03
Art Unit: 1616 Phone Number 308-4646 Serial Number: 10/033,632
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL
2D19 2D14

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Drugs for Spinal Anesthesia

Inventors (please provide full names): Timothy J. Brennan

Earliest Priority Filing Date: 12/26/01

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please search:

6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinolol

-3-carboxylic ~~acide~~ acid according to claim 1. If found please search for use as a pharmaceutical, especially as an anesthesia.

LS Kristin
Acting for TK Page

Thanks

Kanak G.

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MAR 3 2003
TECH CENTER 1600/2900

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****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: Sheryl	NA Sequence (#)		STN	
Searcher Phone #: 308-4499	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up:	Bibliographic		Dr.Link	
Date Completed: 3/7/03	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time:	Other		Other (specify)	

PTO-1590 (1-2000)

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:33:40 ON 07 MAR 2003
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FILE COVERS 1907 - 7 Mar 2003  VOL 138 ISS 11
FILE LAST UPDATED: 6 Mar 2003  (20030306/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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=> d stat que
L39          40 SEA FILE=REGISTRY ABB=ON  PLU=ON  TETRAZOL?(L)ETHYL(L)DECA?(L)C
                ARBOX?
L40      214532 SEA FILE=REGISTRY ABB=ON  PLU=ON  3(W)CARBOX?
L41           8 SEA FILE=REGISTRY ABB=ON  PLU=ON  L39 AND L40
L49           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41


=> d ibib abs hitrn 149 1

L49  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:521728  HCAPLUS
DOCUMENT NUMBER:          137:93757
TITLE:                    Preparation of sulfonylamino- and
                          azolylpyrrolidinylmethylisoquinolinecarboxylates as
                          excitatory amino acid receptor antagonists.
INVENTOR(S):              Bleisch, Thomas John; Filla, Sandra Ann; Ornstein,
                          Paul Leslie
PATENT ASSIGNEE(S):       Eli Lilly and Company, USA
SOURCE:                   PCT Int. Appl., 94 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2002053556      A2   20020711       WO 2001-US45862  20011220
         W:  AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES,
             FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
             MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL,
             TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY,
             KG, KZ, MD, RU
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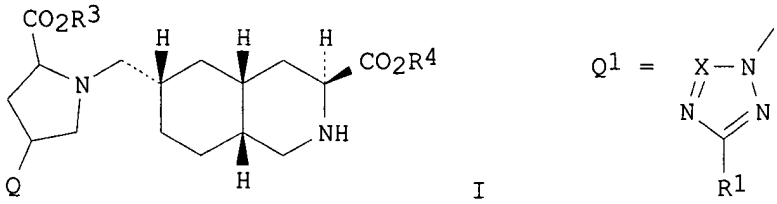
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-259922P P 20010105
OTHER SOURCE(S): MARPAT 137:93757
GI



I

AB Title compds. [I; R1 = H, alkyl, alkoxy, cycloalkyl, SO2R2, SR2, CH2SR2, aryl, aralkyl, (substituted) aryl; R2 = alkyl; R3, R4 = H, alkyl, alkenyl, alkylaryl, alkylcycloalkyl, alkyldialkylamino, alkylpyrrolidinyl, alkylpiperidinyl, alkylmorpholinyl; Q = Q1, R5YSO2NR6; R5 = alkyl, CF3, (substituted) aryl; R6 = H, alkyl, alkylaryl; Y = (CH2)n; n = 0-3; with a proviso], were prepd. for, e.g., treatment of migraine (no data). Thus, Et (3S,4aR,6S,8aR)-6-[[(3S,5S)-5-(ethoxycarbonyl)-3-hydroxypyrrolidinyl]methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (prepn. given), tetrazole, and Ph3P in THF at 0.degree. were treated dropwise with di-Et azodicarboxylate followed by stirring for 18 h at room temp. to give 31% tetrazolylpyrrolidine deriv., which was heated in 6N HCl at 95.degree. for 18 h to give 100% (3S,4aR,6S,8aR)-6-[[(2S,4S)-2-carboxy-4-(tetrazol-1-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid dihydrochloride.

IT **441053-86-7P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-methyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-87-8P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-adamantyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-88-9P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-cyclopentyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-89-0P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-propyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-90-3P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-phenyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-92-5P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-carboxy-4-[5-(1,1-dimethylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid **441053-97-0P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-carboxy-4-(5-ethyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid **441053-98-1P**, (3S,4AR,6S,8aR)-6-[[(2S,4S)-2-carboxy-4-[5-isopropyl-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid dihydrochloride
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of sulfonylamino- and azolylpyrrolidinylmethylisoquinolinecarboxylates as excitatory amino acid receptor antagonists)

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=> fil caold
FILE 'CAOLD' ENTERED AT 10:33:56 ON 07 MAR 2003
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=>
=>

=> s l41
L50 0 L41

=> fil reg
FILE 'REGISTRY' ENTERED AT 10:34:08 ON 07 MAR 2003
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 5 MAR 2003 HIGHEST RN 497055-63-7
DICTIONARY FILE UPDATES: 5 MAR 2003 HIGHEST RN 497055-63-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

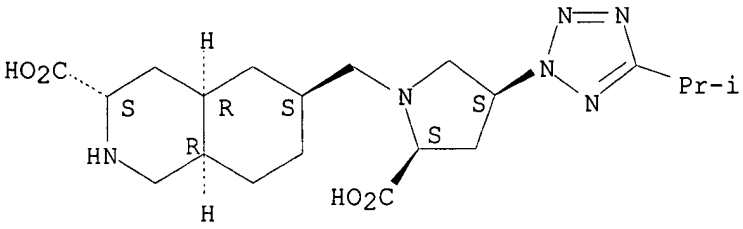
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can l41 tot

L41 ANSWER 1 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-98-1 REGISTRY
CN **3-Isoquinolinecarboxylic acid, 6-[[(2S,4S)-2-carboxy-4-[5-(1-methylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydro-, dihydrochloride, (3S,4aR,6S,8aR)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-carboxy-4-[5-isopropyl-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid dihydrochloride**

FS STEREOSEARCH
MF C20 H32 N6 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



●2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 2 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-97-0 REGISTRY
CN **3-Isoquinolinecarboxylic acid, 6-[[(2S,4S)-2-carboxy-4-(5-ethyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, (3S,4aR,6S,8aR)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-carboxy-4-(5-ethyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid**
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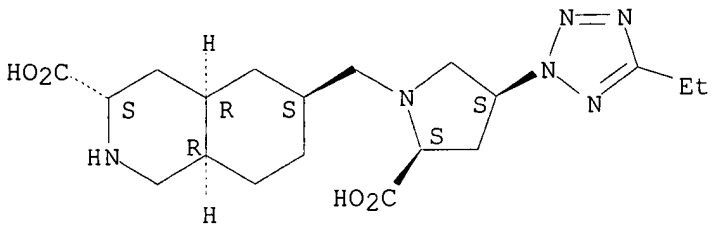
MF C19 H30 N6 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

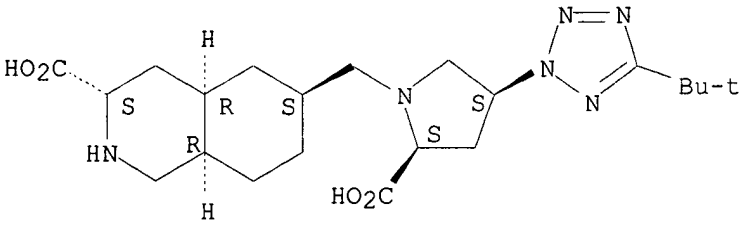
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 3 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-92-5 REGISTRY
CN **3-Isoquinolinecarboxylic acid, 6-[[(2S,4S)-2-carboxy-4-[5-(1,1-dimethylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydro-,**

(3S,4aR,6S,8aR)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-carboxy-4-[5-(1,1-dimethylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid**
FS STEREOSEARCH
MF C21 H34 N6 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 4 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-90-3 REGISTRY
CN **3-Isoquinolinecarboxylic acid, 6-[[(2S,4S)-2-(ethoxycarbonyl)-4-(5-phenyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-phenyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride**
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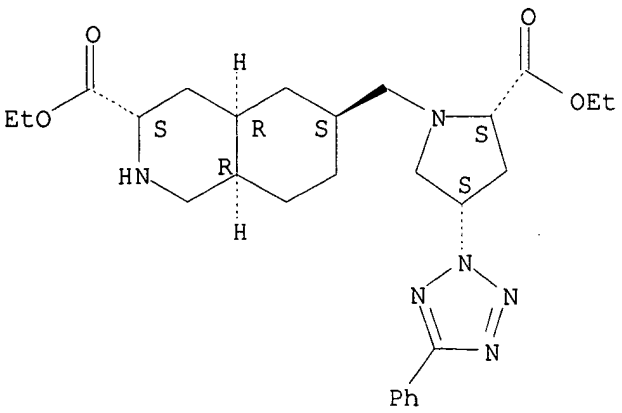
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 5 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-89-0 REGISTRY
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OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-propyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride**
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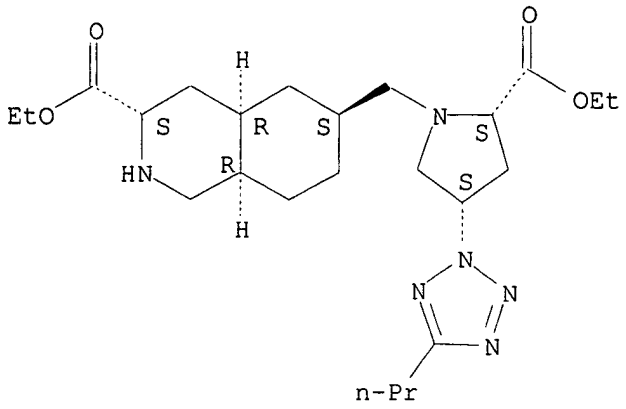
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 6 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-88-9 REGISTRY
CN **3-Isoquinolinecarboxylic acid, 6-[[(2S,4S)-4-(5-cyclopentyl-2H-tetrazol-2-yl)-2-(ethoxycarbonyl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-cyclopentyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride**
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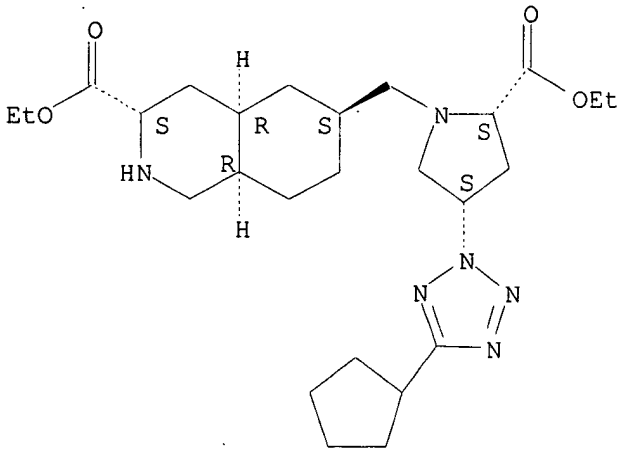
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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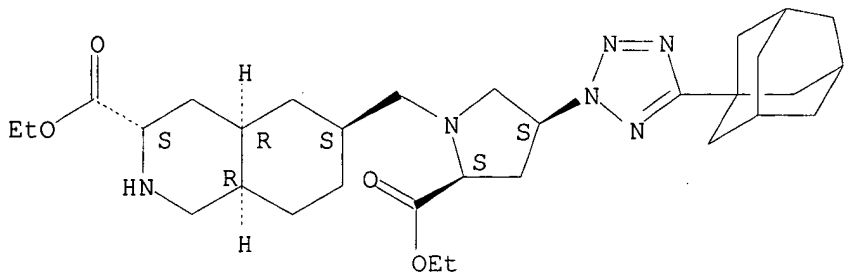
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 7 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-87-8 REGISTRY
CN **3-Isoquinolinecarboxylic acid, 6-[[(2S,4S)-2-(ethoxycarbonyl)-4-(5-tricyclo[3.3.1.13,7]dec-1-yl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-adamantyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride**
FS STEREOSEARCH
MF C31 H48 N6 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 8 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 441053-86-7 REGISTRY
CN **3-Isoquinolinecarboxylic acid, 6-[[(2S,4S)-2-(ethoxycarbonyl)-4-(5-methyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(3S,4AR,6S,8aR)-6-[[(2S,4S)-2-ethoxycarbonyl-4-(5-methyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride**
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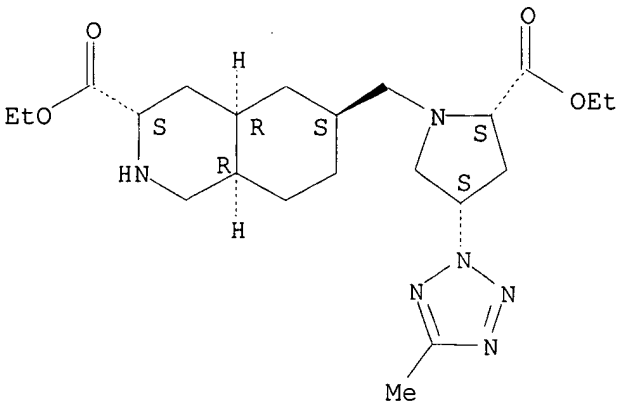
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

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FILE COVERS 1907 - 7 Mar 2003  VOL 138 ISS 11
FILE LAST UPDATED: 6 Mar 2003  (20030306/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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=> d stat que l56
L39          40 SEA FILE=REGISTRY ABB=ON  PLU=ON  TETRAZOL?(L)ETHYL(L)DECA?(L)C
                ARBOX?
L40      214532 SEA FILE=REGISTRY ABB=ON  PLU=ON  3(W)CARBOX?
L41           8 SEA FILE=REGISTRY ABB=ON  PLU=ON  L39 AND L40
L46         323 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DECAHYDROISOQUIN?
L49           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41
L53          66 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L46 AND 3(W)CARBOX?
L54          40 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L53 AND TETRA?
L55          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L54 AND TETRAZOLE(W)5
L56          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L55 NOT L49


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=> d ibib abs hitrn l56 1-11

L56  ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2000:806928  HCAPLUS
DOCUMENT NUMBER:          134:161346
TITLE:                    Role of AMPA and GluR5 kainate receptors in the
                          development and expression of amygdala kindling in the
                          mouse
AUTHOR(S):                Rogawski, M. A.; Kurzman, P. S.; Yamaguchi, S.-i.; Li,
                          H.
CORPORATE SOURCE:         Neuronal Excitability Section, Epilepsy Research
                          Branch, National Institute of Neurological Disorders
                          and Stroke, National Institutes of Health, Bethesda,
                          MD, 20892-1408, USA
SOURCE:                   Neuropharmacology (2000), Volume Date 2001, 40(1),
                          28-35
                          CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal
```

LANGUAGE: English

AB The role of AMPA and GluR5-contg. kainate receptors in the development and expression of amygdala kindling was examd. using the selective 2,3-benzodiazepine AMPA receptor antagonist GYKI 52466 [(1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine] and the **decahydroisoquinoline** mixed AMPA receptor and GluR5 kainate receptor antagonist LY293558 {(3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl]**decahydroisoquinoline-3-carboxylic** acid)}. Administration of GYKI 52466 (5-40 mg/kg, i.p.) and LY293558 (10-40 mg/kg, i.p.) prior to daily kindling stimulation in mice produced a dose-dependent suppression of the rate of development of behavioral kindled seizure activity and reduced the duration of the stimulation-induced electrog. afterdischarge. In drug-free stimulation sessions after the initial drug-treatment sessions, there was an acceleration in the rate of kindling development compared with the rate during the preceding drug-administration period; the "rebound" rate was also greater than the kindling rate in saline-treated control animals. In fully kindled animals, both GYKI 52466 and LY293558 produced a dose-dependent suppression of evoked seizures (ED50, 19.3 and 16.7 mg/kg, resp.). Although AMPA receptors appear to be crit. to the expression of kindled seizures, since kindling development progressed despite the suppression of behavioral seizure activity, AMPA receptors are less important to the kindling process. LY293558 was modestly less effective at suppressing behavioral seizures during kindling and was not superior to GYKI 52466 in retarding the overall extent of kindling development, indicating that GluR5 kainate receptors do not contribute to epileptogenesis in this model.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:304166 HCAPLUS

DOCUMENT NUMBER: 133:218055

TITLE: Kainate receptor-mediated activation of the AP-1 transcription factor complex in cultured rat cerebellar granule cells

AUTHOR(S): Kovacs, A. D.; Cebers, G.; Liljequist, S.

CORPORATE SOURCE: Division of Drug Dependence Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Swed.

SOURCE: Brain Research Bulletin (2000), 52(2), 127-133
CODEN: BRBUDU; ISSN: 0361-9230

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The sequence-specific DNA-binding activity of the AP-1 transcription factor complex was measured in cultured rat cerebellar granule cells by electrophoretic mobility shift assay. A low concn. of kainate (KA; 10 .mu.M), but not .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA; 10 .mu.M), enhanced DNA-binding of the AP-1 transcription factor in cultures pretreated with Con A (Con A), to prevent KA receptor desensitization. In the presence of cyclothiazide (an inhibitor of AMPA receptor desensitization), KA (10 .mu.M) caused only a slight increase of AP-1 DNA-binding, in contrast to the 3-fold enhancement produced by AMPA (10 or 30 .mu.M) or by a higher concn. of KA (30 .mu.M), suggesting that the effect of KA, in the presence of Con A, is mediated by activation of putative KA receptors. To confirm this, the effects of the AMPA receptor-selective, non-competitive antagonist, 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 53655; 50 .mu.M), the mixed AMPA/KA receptor competitive antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 50 .mu.M), and the AMPA and GluR5 KA receptor competitive antagonist, (-)(3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**

-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-**decahydroisoquinoline-3-carboxylic** acid monohydrate (LY 326325; 100 .mu.M), were examd. on AMPA- and KA-induced AP-1 activation, resp. The authors results suggest that stimulation of native KA receptors is responsible for the obsd. KA-specific activation of the AP-1 transcription factor complex.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:704431 HCAPLUS
DOCUMENT NUMBER: 131:317686
TITLE: Synergistic neuroprotective effects by combining an NMDA or AMPA receptor antagonist with nitric oxide synthase inhibitors in global cerebral ischemia
AUTHOR(S): Hicks, C. A.; Ward, M. A.; Swettenham, J. B.; O'Neill, M. J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly & Company, Windlesham, Surrey, UK
SOURCE: European Journal of Pharmacology (1999), 381(2/3), 113-119
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have investigated the neuroprotective effects of combining an NMDA or AMPA receptor antagonist with a nitric oxide synthase (NOS) inhibitor in the gerbil model of global cerebral ischemia. Ischemia was induced by occlusion of the common carotid arteries for 5 min. (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801, 2.5 mg/kg i.p.) or (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)] **decahydroisoquinoline-3-carboxylic** acid (LY293558, 20 mg/kg i.p.) and 7-nitroindazole (25 mg/kg i.p.) or N-[4-(2-{[(3-chlorophenyl)methyl]amino}ethyl) phenyl]-2-thiophenecarboximidamide dihydrochloride (ARL17477, 25 mg/kg i.p.) were administered alone or in combination (i.e., MK-801 with 7-nitroindazole or ARL17477 or LY293558 with 7-nitroindazole or ARL17477). In the present studies, both MK-801 and LY293558 provided significant degree of neuroprotection, while 7-nitroindazole and ARL17477 also provided some neuroprotection, which failed to reach significance in every case. However, the combination of MK-801 with 7-nitroindazole or ARL17477 provided 21% or 44% greater protection than the total protection or either alone. Likewise, the combination of LY293558 with 7-nitroindazole or ARL17477 provided 14.5% and 35% greater protection than total protection of either compd. alone. These results indicate that several pathways contribute to ischemic cell death and combining excitatory amino antagonists and NOS inhibitors provides greater protection than either alone. Therefore, combination therapy should be considered as an approach for treating ischemic conditions.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:693075 HCAPLUS
DOCUMENT NUMBER: 131:335363
TITLE: NMDA receptor antagonism, but not AMPA receptor antagonism attenuates induced ischemic tolerance in the gerbil hippocampus
AUTHOR(S): Bond, Ann; Lodge, David; Hicks, Caroline A.; Ward, Mark A.; O'Neill, Michael J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Company, Surrey, GU20 6PH, UK
SOURCE: European Journal of Pharmacology (1999), 380(2/3), 91-99

CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies have shown that a brief "pre-conditioning" ischemic insult reduces the hippocampal cell death caused by a subsequent more severe test insult. In the present studies, the authors have examd. the effects of the non-competitive NMDA receptor antagonist ((5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, MK-801) a competitive NMDA receptor antagonist, LY202157, AMPA receptor antagonist ((3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole**-**5**-yl)] **decahydroisoquinoline-3-carboxylic** acid, LY293558), a non-competitive AMPA receptor antagonist ((-)-1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-acetyl-2,3-benzodiazepine, LY300164), and a mixed NMDA / AMPA receptor antagonist, LY246492, in a gerbil model of ischemic tolerance. Ischemic tolerance was induced by subjecting gerbils to a 2-min "pre-conditioning" ischemia (bilateral carotid occlusion) 2 days prior to a 3-min test ischemia. The effects of MK-801 (2 mg/kg i.p.), LY293558 (20 mg/kg i.p., followed by 4 .times. 10 mg/kg at 3 h intervals), LY300164 (4 .times. 10 mg/kg i.p. at 1 h intervals), LY246492 (40 mg/kg i.p., followed by 4 .times. 20 mg/kg i.p. at 3 h intervals) and LY202157 (30 mg/kg i.p., followed by 4 .times. 15 mg/kg i.p. at 2 h intervals) were then examd. in this model. Initial dosing commenced 30 min prior to the 2-min "pre-conditioning" ischemia. Results indicated that a 2-min "pre-conditioning" ischemia produced ischemic tolerance in all cases. The non-competitive NMDA receptor antagonist, MK-801, produced a significant ($P < 0.01$) redn. in the induced tolerance, while the competitive NMDA receptor antagonist, LY202157, also attenuated ($P < 0.05$) the induction of tolerance. In contrast, two AMPA receptor antagonists (LY293558 and LY300164) and a mixed NMDA/AMPA receptor antagonist (LY246492) had no effect on the induction of tolerance. These results suggest that NMDA receptor activation, but not AMPA receptor activation is involved in the phenomenon of ischemic tolerance.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:481992 HCAPLUS
DOCUMENT NUMBER: 127:170899

TITLE: (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole**-**5**-yl) ethyl]**decahydroisoquinoline**-**3-carboxylic** acid (LY293558) and its racemate (LY215490): a selective and competitive AMPA/kainate receptor antagonist

AUTHOR(S): Lodge, David; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Res. Centre Ltd., Eli Lilly & Co., Surrey, GU20 6PH, UK

SOURCE: Excitatory Amino Acids: Clinical Results with Antagonists (1997), 81-87, 129-152. Editor(s): Herrling, P. L. Academic: London, UK.
CODEN: 64UIAO
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with over 550 refs. During the structure-activity development of series of **decahydroisoquinoline**-based N-methyl-D-aspartate (NMDA) antagonists, some compds. in the series showed activity at .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Of these, (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole**-**5**-yl)ethyl]decahydroisouinoline-**3-carboxylic** acid (LY293558) (Fig. 1) was one of the most potent and selective for AMPA receptors in vitro and in vivo. LY215490 is the racemic mixt. LY293558 is centrally active following parenteral administration in animals, with

no NMDA receptor antagonist activity at in vivo doses which block AMPA receptors, and a pharmacol. consistent with effects of other known AMPA antagonists. LY293558 possesses neuroprotectant activity against AMPA- and ischemia-induced neuronal injury in multiple animal models including focal ischemia in the rat and cat, and spinal ischemia in the rabbit. Thus, LY293558 may have clin. utility as a neuroprotectant in patients subjected to an ischemic neuronal event that involves glutamate excitotoxicity.

L56 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:706664 HCAPLUS
DOCUMENT NUMBER: 126:1010
TITLE: Selective protection against AMPA- and kainate-evoked neurotoxicity by (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl] **decahydroisoquinoline-3-carboxylic** acid (LY293558) and its racemate (LY215490)
AUTHOR(S): Schoepp, D. D.; Salhoff, C. R.; Fuson, K. S.; Sacaan, A. I.; Tizzano, J. P.; Ornstein, P. L.; May, P. C.
CORPORATE SOURCE: Lilly Research Labs., Eli Lilly Co., Indianapolis, IN, USA
SOURCE: Journal of Neural Transmission (1996), 103(8-9), 905-916
CODEN: JNTRF3; ISSN: 0300-9564
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glutamate receptor-mediated excitotoxicity is linked to the activation of multiple receptors including those activated by .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate. In this study, the novel glutamate receptor antagonist, as its active isomer (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl]**decahydroisoquinoline-3-carboxylic** acid ((-)LY293558) and it's .+-. racemate (LY215490), was examd. for neuroprotectant effects against excitotoxic injury in vitro and in vivo. This agent selectively protected against AMPA and kainate injury in cultured primary rat hippocampal neurons, an in vivo rat striatal neurotoxicity model, and against agonist-evoked seizures in mice. Thus, (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl] **decahydroisoquinoline-3-carboxylic** acid represents a novel receptor selective and potent systemically active AMPA/kainate receptor antagonist for exploring neuroprotection via non-NMDA receptor mechanisms.

L56 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:271752 HCAPLUS
DOCUMENT NUMBER: 125:320
TITLE: Structure-Activity Studies of 6-Substituted **Decahydroisoquinoline-3-carboxylic** Acid AMPA Receptor Antagonists. 2. Effects of Distal Acid Bioisosteric Substitution, Absolute Stereochemical Preferences, and in Vivo Activity
AUTHOR(S): Ornstein, Paul L.; Arnold, M. Brian; Allen, Nancy K.; Bleisch, Thomas; Borromeo, Peter S.; Lugar, Charles W.; Leander, J. David; Lodge, David; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (1996), 39(11), 2232-44
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have explored the excitatory amino acid antagonist activity in a series of **decahydroisoquinoline-3-carboxylic** acids, and within this series found the potent and selective AMPA antagonist (3SR,4aRS,6RS,8aRS)-6-[2-(1H-**tetrazol**-5-yl)ethyl] **decahydroisoquinoline-3-carboxylic** acid (I). In this and the preceding paper, we looked at the structure-activity relationships for AMPA antagonist activity in this series of compds. We have already shown that I had the optimal stereochem. array and that AMPA antagonist activity was maximized for a two-carbon spacer sepg. a **tetrazole** from the bicyclic nucleus. In this paper, we explored the effects of varying the distal acid and the abs. stereochem. preferences of many of these analogs. We looked at a variety of different acid bioisosteres, including 5-membered hetereocyclic acids such as **tetrazole**, 1,2,4-triazole, and 3-isoxazolone; carboxylic, phosphonic, and sulfonic acid; and acyl sulfonamides. Compds. were evaluated in rat cortical tissue for their ability to inhibit the binding of radioligands selective for AMPA ([3H]AMPA), NMDA ([3H]CGS 19755), and kainic acid ([3H]kainic acid) receptors and for their ability to inhibit depolarizations induced by AMPA (40 .mu.M), NMDA (40 .mu.M), and kainic acid (10 .mu.M). A no. of compds. from this and the preceding paper were also evaluated in mice for their ability to block maximal electroshock-induced convulsions and ATPA-induced rigidity in mice.

L56 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:240710 HCAPLUS
DOCUMENT NUMBER: 124:307404
TITLE: Pharmacological discrimination of GluR5 and GluR6 kainate receptor subtypes by (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl] **decahydroisoquinoline-3-carboxylic**-acid
AUTHOR(S): Bleakman, David; Schoepp, Darryle D.; Ballyk, Barbara; Bufton, Hywel; Sharpe, Erica F.; Thomas, Kathy; Ornstein, Paul L.; Kamboj, Rajender K.
CORPORATE SOURCE: Eli Lilly and Company, Lilly Research Centre, Windlesham, Surrey, GU20 6PH, UK
SOURCE: Molecular Pharmacology (1996), 49(4), 581-5
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacol. tools available for the discrimination of kainate receptor subtypes are limited. The authors examd. the effects of (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl] **decahydroisoquinoline-3-carboxylic** acid (LY293558) and 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline (NBQX) on inward currents assocd. with activation of non-N-methyl-D-aspartate (NMDA) receptors in acutely isolated rat cerebellar Purkinje neurons, rat dorsal root ganglion neurons, and human embryonic kidney 293 cells transfected with human glutamate receptors (GluR) 5 and 6. LY293558 and NBQX inhibited kainate-induced currents in cerebellar Purkinje cells, dorsal root ganglion (DRG) neurons, and human GluR5-transfected cells. In contrast, human embryonic kidney 293 cells expressing GluR6 receptors, although blocked by NBQX, were unaffected by LY293558 at concns. of .ltoreq.100 .mu.M. The selective antagonism by LY293558 of GluR5 receptors should allow the detn. of the functional role of GluR5 and GluR6 in more complex systems.

L56 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:10227 HCAPLUS

DOCUMENT NUMBER: 124:106393
TITLE: Effects of **decahydroisoquinoline-3-carboxylic** acid monohydrate, a novel AMPA receptor antagonist, on glutamate-induced Ca2+ responses and neurotoxicity in rat cortical and cerebellar granule neurons
AUTHOR(S): Liljequist, Sture; Cebers, Gvido; Kalda, Anti
CORPORATE SOURCE: Department Clinical Neuroscience, Karolinska Institute, Stockholm, S-17176, Swed.
SOURCE: Biochemical Pharmacology (1995), 50(11), 1761-74
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, we examd. the effects of a novel water-sol., putative AMPA receptor antagonist, (-)(3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-**decahydroisoquinoline-3-carboxylic** acid monohydrate (LY326325), on glutamate-, N-methyl-D-aspartic acid (NMDA), .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-, and kainic acid (KA)-induced elevations of intracellular Ca2+ concns. ([Ca2+]i) and 45Ca2+ uptake, as well as glutamate agonist-induced neurotoxicity in primary cultures of intact rat cortical and cerebellar granule neurons. In some expts., the actions of LY326325 were tested in the presence of cyclothiazide, a compd. that is known to block glutamate-induced desensitization of AMPA-preferring subtypes of glutamate receptors, thereby largely potentiating the functional effects of AMPA. LY326325 fully blocked the elevations of [Ca2+]i induced by NMDA and non-NMDA glutamate receptor agonists in both cortical and cerebellar granule neurons. The application of increasing concns. of cyclothiazilde was not able to reverse the LY326325-induced blockade of glutamate receptors in cortical neurons. In contrast, the same cyclothiazide treatment fully reversed the blockade produced by the noncompetitive AMPA/KA receptor antagonist 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine HCl (GYKI 52466). In 45Ca2+ uptake studies. LY325325 inhibited the NMDA-, AMPA-, and KA-induced enhancement of 45Ca2+ uptake in a concn.-dependent fashion in both cortical and cerebellar granule cells. In analogy to the results obtained with [Ca2+]i recordings, cyclothiazide failed to counteract the LY326325-induced blockade of KA-stimulated 45Ca2+ uptake in cerebellar granule neurons, whereas the blockade induced by the noncompetitive AMPA/KA receptor blocking agent GYKI 52466 was fully reveresed by cyclothiazide. Because a similar, although no identical pattern of actions was seen following the application of the competitive AMPA/KA receptor antagonist 6-nitro-7-sulphamoyl-benzo(f)quinoxaline-2-3-dione (NBQX), it is suggested that the inhibitory actions of LY326325 are similar to those produced by NBQX but clearly differ from those caused by the noncompetitive AMPA/KA receptor antagonist GYKI 52466. Finally, when the neuroprotective actions of LY326325 on glutamate agonist-induced neurotoxicity were examd. in cerebellar granule neurons, we found that LY326325 almost completely blocked the neurotoxic actions of NMDA, AmPA, and KA, resp., whereas it produced only a partial blockade of glutamate-induced neurotoxicity. Taken together, our current results suggest that although LY326325 blocked both nonNMDA and NMDA-induced Ca2+ responses, it still displayed a preferential affinity for nonNMDA receptors as compared to NMDA receptors. However, LY326325 appears to be a less selective AMPA/KA receptor antagonist than NBQX and GYKI52466, resp.

L56 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:827899 HCAPLUS
DOCUMENT NUMBER: 123:246679
TITLE: In vitro and in vivo antagonism of AMPA receptor activation by (3S,4aR,5R,8aR)-6-[2-(1(2H)-**tetrazole-5**-yl)ethyl]

decahydroisoquinoline-3-carboxylic acid
AUTHOR(S): Schoepp, D. D.; Lodge, D.; Bleakman, D.; Leander, J. D.; Tizzano, J. P.; Wright, R. A.; Palmer, A. J.; Salhoff, C. R.; Ornstein, P. L.
CORPORATE SOURCE: Lilly Res. Lab., Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Neuropharmacology (1995), 34(9), 1159-68
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The in vitro and in vivo pharmacol. of a structurally novel competitive antagonist for the .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subtype of excitatory amino acid receptors is described. LY215490, (.+-.)(6-(2-(1-H-**tetrazol**-5-yl)ethyl) **decahydroisoquinoline-3-carboxylic** acid), was shown to displace selectively 3H-AMPA and 3H-6-cyano-y-nitro-quinoxaline-2,3-dione (3H-CNQX) binding to rat brain membranes. LY215490 potently antagonized quisqualate-and AMPA-induced depolarization of rat cortical slices in a competitive manner, while requiring higher concns. to antagonize the effects of N-methyl-D-aspartate (NMDA) and kainate. In slices of rat hippocampus, LY215490 also selectively antagonized AMPA-evoked release of 3H-norepinephrine. These AMPA receptor activities were due to the (-) isomer of the compd., (3S,4aR,6R,8aR)-6-[2-(1(2-H-**tetrazole-5**-yl)ethyl]**decahydroisoquinoline-3-carboxylic** acid (LY293558). LY215490 was centrally active following parenteral administration in mice as demonstrated by protection vs. maximal electroshock seizures and decreases in spontaneous motor activity. LY215490 (its active isomer being LY293558) represents a novel pharmacol. agent for in vitro and in vivo studies of AMPA receptor function in the CNS.

L56 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:348838 HCAPLUS
DOCUMENT NUMBER: 122:151230
TITLE: The neuroprotective effects of the **decahydroisoquinoline**, LY 215490; a novel AMPA antagonist in focal ischemia
AUTHOR(S): Gill, R.; Lodge, D.
CORPORATE SOURCE: R. Vet. Coll., Dep. Vet. Basic Sci., London, NW1 0TU, UK
SOURCE: Neuropharmacology (1994), 33(12), 1529-36
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LY 215490 (3RS,4aRS,6RS,8aRS-6-[2-(1(2)H-**tetrazole-5**-yl)ethyl]**decahydroisoquinoline-3-carboxylic** acid), a novel, selective, competitive and systemically active AMPA receptor antagonist was tested as a neuroprotective agent against focal ischemia in a model of permanent MCA occlusion in the rat. LY 215490 was administered at a dose of 10, 30 or 100 mg/kg 30 min prior to and post-MCA occlusion. The animals were allowed to survive for 24 h, following which time the brains were processed for volumetric anal. of the infarct size. The low dose of LY 215490 was not effective against the infarct vol. in the hemisphere, cortex or caudate. The 2 .times. 30 mg/kg dose of LY 215490 resulted in 25 and 31% protection against the vol. of hemispheric and cortical ischemic damage, resp. The highest dose of LY 215490 resulted in a reduced neuroprotective effect with 23 and 27% protection against the vol. of hemispheric and cortical ischemic damage, resp. The slightly reduced neuroprotective effect of the highest dosing regimen may be due to the respiratory problems seen with this dose. Neither of the

two neuroprotective doses of LY 215490 produced any redn. in the vol. of caudate damage which represents the core of the infarct.

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in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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L57           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  LY(W)(293558 OR 215490)


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L57  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2003 ACS
RN   154652-83-2  REGISTRY
CN   3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-,
     (3S,4aR,6R,8aR)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-,
     [3S-(3.alpha.,4a.alpha.,6.beta.,8a.alpha.)]-
OTHER NAMES:
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FS   STEREOSEARCH
DR   150131-78-5
MF   C13 H21 N5 O2
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS,
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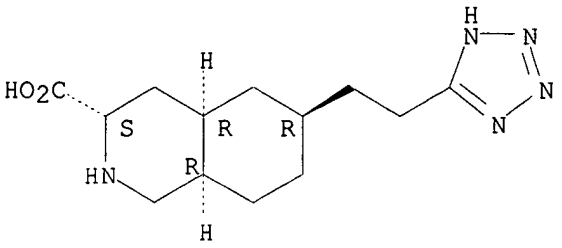

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58 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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REFERENCE 2: 138:117562

REFERENCE 3: 137:273227

REFERENCE 4: 136:79570

REFERENCE 5: 136:493

REFERENCE 6: 135:170886

REFERENCE 7: 135:137466

REFERENCE 8: 134:275608

REFERENCE 9: 134:54906

REFERENCE 10: 133:305610

L57 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 150010-68-7 REGISTRY
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3.alpha.,4a.alpha.,6.beta.,8a.alpha.)-(.+-.)-
OTHER NAMES:
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3.alpha.,4a.alpha.,6.beta.,8a.alpha.)-
CN **LY 215490**
FS STEREOSEARCH
MF C13 H21 N5 O2
SR CA
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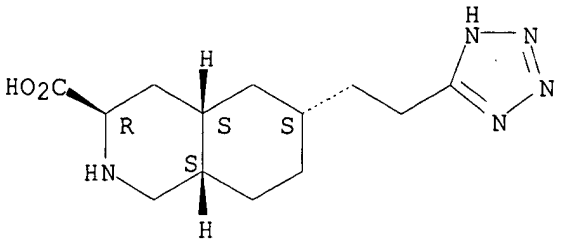
Relative stereochemistry.



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14 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
14 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:95462

REFERENCE 2: 133:247292

REFERENCE 3: 132:58931

REFERENCE 4: 131:54231

REFERENCE 5: 129:23447

REFERENCE 6: 128:212404

REFERENCE 7: 127:170899

REFERENCE 8: 126:1010

REFERENCE 9: 123:329860

REFERENCE 10: 123:246679

=> fil hcaplus
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FILE LAST UPDATED: 6 Mar 2003 (20030306/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d stat que l60
L39 40 SEA FILE=REGISTRY ABB=ON PLU=ON TETRAZOL?(L)ETHYL(L)DECA?(L)C ARBOX?
L40 214532 SEA FILE=REGISTRY ABB=ON PLU=ON 3(W)CARBOX?
L41 8 SEA FILE=REGISTRY ABB=ON PLU=ON L39 AND L40
L46 323 SEA FILE=HCAPLUS ABB=ON PLU=ON DECAHYDROISOQUIN?
L49 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L41
L53 66 SEA FILE=HCAPLUS ABB=ON PLU=ON L46 AND 3(W)CARBOX?
L54 40 SEA FILE=HCAPLUS ABB=ON PLU=ON L53 AND TETRA?
L55 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L54 AND TETRAZOLE(W)5
L56 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L55 NOT L49
L57 2 SEA FILE=REGISTRY ABB=ON PLU=ON LY(W)(293558 OR 215490)
L58 64 SEA FILE=HCAPLUS ABB=ON PLU=ON L57
L59 55 SEA FILE=HCAPLUS ABB=ON PLU=ON L58 NOT (L56 OR L49)
L60 18 SEA FILE=HCAPLUS ABB=ON PLU=ON L59 AND (SPIN? OR ANEST? OR PAIN? OR ANALGES?)

=> d ibib abs hitrn l60 1-18

L60 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:570979 HCAPLUS
DOCUMENT NUMBER: 138:117562
TITLE: Effect of intrathecal non-NMDA EAA receptor antagonist LY293558 in rats a new class of drugs for **spinal anesthesia**
AUTHOR(S): Von Bergen, Nicholas H.; Subieta, Alberto; Brennan, Timothy J.
CORPORATE SOURCE: University of Iowa College of Medicine, Iowa City, IA, 52242-1079, USA
SOURCE: Anesthesiology (2002), 97(1), 177-182
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Excitatory amino acid receptors are important for both sensory and motor function in the **spinal** cord. We studied the effects of intrathecal LY293558, a competitive non-N-methyl-D-aspartate excitatory amino acid receptor antagonist, on motor and sensory function in rats to det. whether drugs blocking these receptors could potentially be used as alternative agents to local **anesthetics** for **spinal anesthesia**. Rats were tested before and 15-240 min after intrathecal injection of 5 nmol (in 10 .mu.l) LY293558. Sensory function was tested at the hind paw using withdrawal response to pin prick and withdrawal to pinch with sharp forceps. Motor performance (ambulation, placing reflex, and Rotorod time), blood pressure, and heart rate were also evaluated. Some tests were repeated the next day. Responses after LY293558 were compared to injection of 40 .mu.l bupivacaine, 0.75%. Pin-prick responses at the forepaw, chest, abdomen, hind leg, and hind paw were also examd. after intrathecal LY293558. Intrathecal LY293558 blocked both sensory and motor responses through 180 min; complete recovery was present the following day. No change in blood pressure or heart rate occurred. The effects of LY293558 were more pronounced and sustained than those of bupivacaine. Segmental blockade of the response to pin prick was present after LY293558. Drugs like LY293558 that block .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate receptors may be an alternative to local **anesthetics** for **spinal anesthesia** in humans.
IT **154652-83-2**, LY293558

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of intrathecal non-NMDA EAA receptor antagonist LY293558 in rats a new class of drugs for **spinal anesthesia**)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:801702 HCAPLUS
DOCUMENT NUMBER: 136:95462
TITLE: LY-293558(Eli Lilly & Co)
AUTHOR(S): Gilron, Ian
CORPORATE SOURCE: Departments of Anesthesiology and Pharmacology & Toxicology, Kingston General Hospital, Queen's University, Kingston, ON, K7L 2V7, Can.
SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2001), 2(9), 1273-1278
CODEN: COIDAZ
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Lilly is developing the racemic compd. LY-215490, a selective and competitive AMPA antagonist, as a potential treatment for cerebral infarction, cerebrovascular ischemia, epilepsy and as an **analgesic** [135089], [158980], [254029], [278691]. By Jan. 2000, LY-293558 was undergoing phase II trials for **pain** [414000].
IT **150010-68-7**, LY-215490
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(LY-215490: AMPA antagonist for **analgesia**)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:370555 HCAPLUS
DOCUMENT NUMBER: 136:79570
TITLE: Can novel AMPA and NMDA receptor antagonists induce **analgesia**?
AUTHOR(S): Uchikawa, Tomoyoshi; Kiuchi, Yuji; Kindscher, James; Oguchi, Katsuji; Goto, Hiroshi
CORPORATE SOURCE: Orthopedic Surgery, Showa University Fujigaoka Hospital, Yokohama, 227-8501, Japan
SOURCE: Showa University Journal of Medical Sciences (2000), 12(3), 235-240
CODEN: SUMSEG; ISSN: 0915-6380
PUBLISHER: Showa Medical Association and Showa University
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The glutamate receptors in the nervous system are related to nociceptive response. These receptors include the AMPA (.alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor and the NMDA (N-methyl-D-aspartate) receptor. The purpose of this study was to investigate whether novel antagonists of these glutamate receptors could inhibit the nociceptive response in the **spinal** cord of male Wistar rats. Rats intrathecally (i.t.) received 0.1 to 10 pmol of Ly-293558 (a novel AMPA antagonist) and 10 to 1000 pmol of Ly-233053 (a novel NMDA antagonist) dissolved in 50 .mu.l of physiol. saline. A 50 .mu.l vol. of 2.0% formalin soln. was injected as a noxious stimulus into the hindpaw 15 min after the i.t. injections. We measured the total time the animal spent licking the hindpaw in the first 5 min (early phase) and from 10 to 30 min (late phase) after formalin injection. Controlled total licking time was 103 .+-. 13 s (mean .+-. SE) (early phase) and 151 .+-. 86 s (late phase). The licking time during the early phase was significantly and

dose-dependently decreased with intrathecal administrations of both Ly-293558 and Ly-233053 ($p < 0.05$). However, Ly-293558 induced this effect at much lower concns. During the late phase, only the highest dose of each antagonist significantly shortened licking time. Our results indicate that these two novel AMPA and NMDA receptor antagonists when intrathecally administrated could induce antinociceptive effects during both the acute phase (peripheral sensitization) and late phase (central sensitization) of formalin-induced nociceptive stimulation without producing motor dysfunction.

IT **154652-83-2**, Ly-293558
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(can novel AMPA and NMDA receptor antagonists induce **analgesia**
)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:717381 HCAPLUS
DOCUMENT NUMBER: 134:275608
TITLE: Effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative **pain**
AUTHOR(S): Gilron, Ian; Max, Mitchell B.; Lee, Gloria; Booher, Susan L.; Sang, Christine N.; Chappell, Amy S.; Dionne, Raymond A.
CORPORATE SOURCE: Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, the Department of Nursing, NIH Clinical Center, National Institutes of Health, Bethesda, MD, 20892-1258, USA
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis) (2000), 68(3), 320-327
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Previous studies suggest that 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate antagonists reduce exptl. induced **pain**. There have been no studies of AMPA/kainate antagonists in clin. **pain**. Methods: **Analgesic** efficacy of i.v. LY293558 (0.4 or 1.2 mg/kg) was compared with that of i.v. ketorolac tromethamine (INN, ketorolac; 30 mg) and placebo in a randomized, double-blind, parallel-group study after oral surgery (n = 70). Study drugs were administered at the onset of moderate **pain**; **pain** intensity and relief were measured for 240 min. Results: High-dose LY293558 and ketorolac tromethamine were superior to placebo ($P < .05$) for **pain** evoked by mouth opening and one of several measures of spontaneous **pain**: SPID240 .+-. SEM for **pain** evoked by mouth opening was highest for ketorolac tromethamine (151 .+-. 58), intermediate for high-dose LY293558 (-45 .+-. 35), and least for low-dose LY293558 (-151 .+-. 39) and placebo (-162 .+-. 50). High-dose LY293558 was superior to placebo at individual time points (45 to 240 min) for **pain** evoked by mouth opening but not for spontaneous **pain**. The spontaneous summed **pain** intensity difference over 240 min (SPID240 .+-. SEM) was highest for ketorolac tromethamine (303 .+-. 84), intermediate for high-dose LY293558 (-51 .+-. 40) and low-dose LY293558 (-96 .+-. 45), and least for placebo (-180 .+-. 24). LY293558 was well tolerated, with dose-dependent and reversible side effects including hazy vision in 20% of patients and sedation in 15%. Conclusions: This is the first evidence that an AMPA/kainate antagonist reduces clin. **pain**. Tests of evoked **pain** may be more sensitive to certain **analgesics** than those of spontaneous **pain**. The evaluation of evoked **pain** as an outcome

measure in **analgesic** trials may identify potentially useful compds. otherwise missed if only spontaneous **pain** is evaluated.

IT **154652-83-2**, LY293558
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative **pain** in humans)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:263975 HCAPLUS
DOCUMENT NUMBER: 133:38538
TITLE: Effects of glutamate receptor antagonists on lower urinary tract function in conscious unanesthetized rats
AUTHOR(S): Nishizawa, Oamu; Igawa, Yasuhiko; Satoh, Tomoya; Yamashiro, Seiji; Sugaya, Kimio
CORPORATE SOURCE: Department of Urology, Shinshu University School of Medicine, Matsumoto City, 390, Japan
SOURCE: Advances in Experimental Medicine and Biology (1999), 462(Advances in Bladder Research), 275-281
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies were carried out to study the effects of the intrathecal administered glutamate receptor antagonists on the bladder and urethral activities during isovolumetric bladder contraction in conscious normal and chronic **spinal** rats. Twenty-eight female Wistar rats with and without previous **spinal** cord transection were used. Before and after intrathecal administration of glutamate receptor antagonist, urodymamic parameters under isovolmetric condition of the bladder were analyzed. In normal rats, MK-801 (noncompetitive N-methyl-D-aspartate [NMDA] receptor antagonist) and LY 293558 (competitive AMPA receptor antagonist) produced a decrease in bladder contraction pressure and urethral activity with dose dependent manner. In chronic **spinal** rats, detrusor-sphincter dyssynergia (DSD) was developed before drug administration. MK-801 and LY 293558 partially inhibited bladder contraction pressure, and markedly depressed urethral contraction concomitant with bladder contraction. LY 293558 produced urethral relaxation concomitant with bladder contraction. Thus, in both normal rats and chronic **spinal** rats, two subtypes of glutamate receptors (NMDA and AMPA receptors) in the **spinal** cord were involved in the control of bladder and urethral activities. The AMPA receptor in the **spinal** cord seems to take an important role in the development of DSD.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intrathecal glutamate receptor antagonists effect on bladder and urethral activities during isovolumetric bladder contraction in conscious normal and chronic **spinal** rats)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:34733 HCAPLUS
DOCUMENT NUMBER: 132:88184
TITLE: Inhibitors of the interaction of glutamate with the

AMPA and/or kainate receptor complex for treatment of demyelinating disorders
INVENTOR(S): Turski, Lechoslaw; Smith, Terence
PATENT ASSIGNEE(S): Eisai Co., Ltd, Japan
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001376	A2	20000113	WO 1999-GB2112	19990702
WO 2000001376	A3	20010322		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1100504	A2	20010523	EP 1999-929545	19990702
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002519373	T2	20020702	JP 2000-557823	19990702

PRIORITY APPLN. INFO.: GB 1998-14380 A 19980702
GB 1998-24393 A 19981106
WO 1999-GB2112 W 19990702

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of demyelinating disorders. Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compns.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of interaction of glutamate with AMPA and/or kainate receptor complex for treatment of demyelinating disorders)

L60 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:581904 HCAPLUS
DOCUMENT NUMBER: 132:58931
TITLE: Influence of Glutamate Receptor Antagonists on Micturition in Rats with **Spinal** Cord Injury
AUTHOR(S): Yoshiyama, Mitsuharu; Nezu, Frank M.; Yokoyama, Osamu; Chancellor, Michael B.; de Groat, William C.
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261, USA
SOURCE: Experimental Neurology (1999), 159(1), 250-257
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study was undertaken to det. if an AMPA (LY215490) or an NMDA (MK-801) glutamatergic receptor antagonist can reduce urinary tract dysfunctions related to detrusor hyperreflexia and detrusor-sphincter dyssynergia in awake, **spinal** cord-injured (SCI) rats. Expts. were performed on female Sprague-Dawley rats in which the **spinal** cord was completely transected at T8-10 level, 2-3 wk prior to performing an intravesical continuous infusion cystometrogram (CMG). Bladder vol. threshold (VT) for inducing voiding and voiding efficiency (VE) were detd. by measuring voided vols. and residual vols. (RV). After control CMGs were performed, cumulative i.v. doses of LY215490 (0.1, 1, and 10 mg/kg) or MK-801 (0.03, 0.3, and 3 mg/kg) were administered at 120-min intervals. Small doses of LY215490 (0.1 mg/kg) or MK-801 (0.03 and 0.3 mg/kg) did not

affect any parameters. A large dose (10 mg/kg) of LY215490 decreased maximal voiding pressure (MVP) by 27% and increased RV by 119% and VT by 58% but did not decrease VE. The highest cumulative dose (3 mg/kg) of MK-801 significantly increased RV by 134% and VT by 44% and markedly decreased VE by 60% and MVP by 18%. The effects of LY215490 to reduce MVP and increase VT without changing VE suggest that an AMPA receptor antagonist might be useful in treating detrusor-sphincter dyssynergia and bladder hypertrophy after SCI. The effect of MK-801 to markedly reduce VE indicates that NMDA receptor antagonists may exacerbate neurogenic bladder dysfunction in SCI patients. (c) 1999 Academic Press.

IT **150010-68-7**, LY215490
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of glutamate receptor antagonists on micturition in rats with **spinal** cord injury)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:256179 HCAPLUS
DOCUMENT NUMBER: 131:54231
TITLE: Effects of N-methyl-D-aspartate (dizocilpine) and .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (LY215490) receptor antagonists on the voiding reflex induced by perineal stimulation in the neonatal rat
AUTHOR(S): Yoshiyama, M.; Erickson, K. A.; Erdman, S. L.; De Groat, W. C.
CORPORATE SOURCE: School of Medicine, Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: Neuroscience (Oxford) (1999), 90(4), 1415-1420
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was undertaken to examine the role of .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate and N-methyl-D-aspartate glutamate receptors in the regulation of voiding reflexes induced by perineal stimulation in the neonatal rat. Four-, six- and 10-day-old awake rats were used in the expts. and perineal stimulation was applied using the tip of a 1-mL syringe to evoke voiding. Voided vol. and residual vol. were measured. In 10-day-old rats, LY215490 (3-10 mg/kg, i.p.), a competitive .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor antagonist, significantly inhibited reflex voiding, increasing the residual vol. 34-53-fold. A 3 mg/kg dose decreased the urine release by 55%, whereas 10 mg/kg totally suppressed the voiding reflex induced by the perineal stimulation. LY215490 (10 mg/kg, i.p.) produced similar effects in four- and six-day-old rats. Dizocilpine (1-3 mg/kg, i.p.), a non-competitive N-methyl-D-aspartate receptor antagonist, also significantly decreased the urine release (62-82%) and increased residual vol. (180-230-fold). Combined administration of LY215490 (1 mg/kg, i.p.) and dizocilpine (0.3 mg/kg, i.p.) to 10-day-old rats, in doses that individually had no effect on perineal stimulation-evoked voiding, depressed voided vol. by 65%. These results indicate that, in neonatal rats, glutamatergic transmission in the **spinal** cord has an essential role in reflex micturition induced by perineal stimulation, and that facilitatory interactions between .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate and N-methyl-D-aspartate glutamatergic mechanisms are important for voiding, as noted previously in adult rats.

IT **150010-68-7**, LY215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(glutaminergic receptor in regulation of micturition induced by perineal stimulation in development response to)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:779038 HCAPLUS
DOCUMENT NUMBER: 130:134099
TITLE: Decahydroisoquinolines: novel competitive AMPA/kainate antagonists with neuroprotective effects in global cerebral ischemia
AUTHOR(S): O'Neill, Michael J.; Bond, Ann; Ornstein, Paul L.; Ward, Mark A.; Hicks, Caroline A.; Hoo, Ken; Bleakman, David; Lodge, David
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Co. Ltd., Windlesham, GU20 6PH, UK
SOURCE: Neuropharmacology (1998), 37(10-11), 1211-1222
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, the activity of a series of glutamate receptor antagonists from the decahydroisoquinoline group of compds. both in vitro and in vivo, are evaluated. Compd. activity at .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors was assessed using ligand binding to cloned iGluR2 and iGluR5 receptors and on responses evoked by AMPA and N-methyl-D-aspartate (NMDA) in the cortical wedge prepn. In vivo, compds. were examd. for antagonist activity electrophysiol. in the rat **spinal** cord prepn. and in the gerbil model of global cerebral ischemia. Compds. tested were LY293558, which has been shown to protect in models of focal cerebral ischemia, LY202157 (an NMDA antagonist), LY246492 (an NMDA and AMPA receptor antagonist), LY302679, LY292025, LY307190, LY280263, LY289178, LY289525, LY294486 (AMPA/kainate antagonists) and LY382884 (an iGluR5 selective antagonist). Results obtained support a role for AMPA receptors in cerebral ischemia. LY377770 (a mixed AMPA/iGluR5 antagonist and active isomer of LY294486) demonstrated good neuroprotection with a 2-h time window and may therefore be useful in the treatment of ischemic conditions.
IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(decahydroisoquinoline competitive AMPA/kainate antagonists with neuroprotective effects in global cerebral ischemia)
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:763613 HCAPLUS
DOCUMENT NUMBER: 130:163073
TITLE: AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not **pain** in normal skin in humans
AUTHOR(S): Sang, Christine N.; Hostetter, Meredith P.; Gracely, Richard H.; Chappell, Amy S.; Schoepp, Darryle D.; Lee, Gloria; Whitcup, Scott; Caruso, Rafael; Max, Mitchell B.
CORPORATE SOURCE: NIDR/NIH Pain Research Clinic, Pain and Neurosensory Mechanisms Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD, USA
SOURCE: Anesthesiology (1998), 89(5), 1060-1067
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Animal studies suggest that .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-kainate (AMPA-KA) receptors are involved in **pain** processing. The effects of the competitive AMPA-KA antagonist LY293558 in two types of exptl. **pain** in human volunteers, brief **pain** sensations in normal skin, and mech. allodynia-pinprick hyperalgesia were studied after the injection of intradermal capsaicin. Brief i.v. infusions of the competitive AMPA-KA antagonist LY293558 were given to 25 healthy volunteers to examine acute toxicity and **analgesic** effects. Fifteen volunteers then entered a double-blinded, three-period crossover study. In a Phase II study, LY293558 infusions (100% maximally tolerated dose vs. 33% maximally tolerated dose vs. placebo) began 10 min after intradermal injection of 250 .mu.g capsaicin in volar forearm. Spontaneous **pain**, areas of mech. allodynia and pinprick hyperalgesia, and side effects were detd. every 5 min for 60 min. The median maximally tolerated dose was 1.3.+-.0.4 (range, 0.9-2.0) mg/kg. Tests of cognitive and neurol. function were unchanged. Dose-limiting side effects were hazy vision in 95% of volunteers and sedation in 40%. There were no significant changes in elec. or warm-cool detection and **pain** thresholds or heat **pain** thresholds. LY293558 had little effect on brief **pain** sensations in normal skin. Both high and low doses of LY293558 significantly reduced **pain** intensity, **pain** unpleasantness, and the area in which light brush evoked **pain** after intradermal capsaicin. There was a trend toward a dose-response effect of LY293558 on the area in which pinprick evoked **pain** after intradermal capsaicin, which did not reach statistical significance. The authors infer that AMPA-KA receptor blockade reduces the **spinal** neuron sensitization that mediates capsaicin-evoked **pain** and allodynia. The low incidence of side effects at EDs of LY293558 suggests that this class of drugs may prove to be useful in clin. **pain** states.
IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not **pain** in normal skin in humans)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:441022 HCAPLUS
DOCUMENT NUMBER: 129:170935
TITLE: Kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat
AUTHOR(S): Simmons, Rosa Maria A.; Li, Dominic L.; Hoo, Ken H.; Deverill, Michelle; Ornstein, Paul L.; Iyengar, Smriti
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly, Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Neuropharmacology (1998), 37(1), 25-36
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To study the roles of the AMPA and kainate subtypes of non-NMDA glutamate receptors in the processing of persistent nociceptive information, compds. with varying activities at these receptors were examd. for effects on the formalin-induced paw-licking behavior in rats. The selective AMPA antagonist, LY300164 and the mixed AMPA/kainate antagonist, NBQX, were compared for their effects on formalin-induced **pain** behavior. NBQX (3, 10, 20 mg/kg, i.p.), caused antinociception as well as ataxia,

whereas the selective AMPA antagonist, LY300164 (3,5,10 mg/kg, i.p.), did not cause antinociception at doses that did not produce ataxia. In view of the well documented distribution of kainate receptors on C fibers and of the kainate-preferring iGluR5 subtype on dorsal root ganglia (DRG), the authors tested a series of three decahydroisoquinolines with different profiles of activity between iGluR5 and AMPA receptors and all without activity on iGluR6, iGluR7 or KA2 subtypes. LY293558 (0.1, 1, 3, 5 mg/kg, i.p.), which had low micromolar affinity for both iGluR5 and 2 caused, like NBQX, both antinociceptive and ataxic effects. However, the selective iGluR5 antagonist LY382884 (5, 10, 30, 100 mg/kg, i.p.), exhibited antinociceptive actions without ataxia while the iGluR2 preferring antagonist LY302679 (5 mg/kg, i.p), caused ataxia but did not produce antinociceptive effects at that dose. These actions were stereoselective since the enantiomeric compds., LY293559 and LY302680, were ineffective in these tests. The data strongly suggest an involvement of iGluR5 in the processing of nociceptive information.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:323132 HCAPLUS
DOCUMENT NUMBER: 129:23447
TITLE: A method for treating tension-type headache
INVENTOR(S): Olesen, Jes; Bendtsen, Lars; Jensen, Rigmor; Madsen, Ulf
PATENT ASSIGNEE(S): Olesen, Jes, Den.; Bendtsen, Lars; Jensen, Rigmor; Madsen, Ulf
SOURCE: PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9819674	A2	19980514	WO 1997-DK502	19971104
WO 9819674	A3	19980716		
W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, ES, FI, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9748632	A1	19980529	AU 1997-48632	19971104
AU 734490	B2	20010614		
EP 1011656	A2	20000628	EP 1997-911150	19971104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1132082	A1	20010912	EP 2000-204625	19971104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6284794	B1	20010904	US 1999-304115	19990504
US 2002072543	A1	20020613	US 2001-941855	20010830

PRIORITY APPLN. INFO.: DK 1996-1243 A 19961105

US	1996-30294P	P 19961105
EP	1997-911150	A3 19971104
WO	1997-DK502	W 19971104
US	1998-85413P	P 19980514
US	1999-304115	A3 19990504

AB Tension-type headache is treated by interacting with neuronal transmission in relation to **pain** in connection with headache in a way which prevents or decreases sensitization of second order nociceptive neurons. In particular, treatment is performed by administration of an effective amt. of a substance which prevents or decreases central sensitization. Important examples of such substances are substances which interact with glutamate neurotransmission, such as glutamate receptor antagonists. Other examples are e.g. substances which interact with nitric oxide, such as nitric oxide synthase (NOS) inhibitors. According to a broader aspect of the invention, tension-type headache is treated by administration of substances which are effective in preventing or decreasing **pain** in connection with tension-type headache. An addnl. aspect of the invention relates to treatment of tension-type headache by administration of substances which substantially inhibit the activity of NOS. Evidence for central sensitization in chronic myofascial **pain**, as well as mechanisms of spontaneous tension-type headaches, are also described. Gabapentin and dextromethorphen had a prophylactic effect on chronic tension-type headaches.

IT **150010-68-7**, LY 215490 **150010-68-7D**, LY 215490, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tension-type headache treatment)

L60 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1998:26492 HCAPLUS
DOCUMENT NUMBER:	128:149482
TITLE:	The competitive .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist LY293558 attenuates and reverses **analgesic** tolerance to morphine but not to delta or kappa opioids
AUTHOR(S):	Kest, Benjamin; McLemore, Gabrielle; Kao, Bernard; Inturrisi, Charles E.
CORPORATE SOURCE:	Department of Pharmacology, Cornell University Medical College, New York, NY, USA
SOURCE:	Journal of Pharmacology and Experimental Therapeutics (1997), 283(3), 1249-1255 CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER:	Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Antagonists of the NMDA type of excitatory amino acid (EAA) receptor attenuate or reverse the development of tolerance to the **analgesic** effects of the .mu. opioid agonist morphine, the .delta.-1 opioid agonist DPDPE but not the .kappa.-1 agonist U50488H or the .kappa.-3 agonist naloxone benzoylhydrazone. The role of the AMPA subtype of EAA receptor in **analgesic** tolerance was examd. using LY293558, a selective competitive antagonist that is active after systemic administration. Administration of morphine, DPDPE, or U50488H three times daily for 3 days according to an escalating dosing schedule resulted in **analgesic** tolerance as indicated by an increase in **analgesic** ED50 values using the tail-flick test in mice. **Analgesic** tolerance was attenuated when mice received a continuous s.c. infusion of LY293558 at doses of 30, 45 or 60 mg/kg/24 h via an osmotic pump concurrent with the morphine treatment. Continuous s.c. infusion of LY293558 (45 mg/kg/24 h) also reversed established morphine tolerance. In contrast, continuous s.c. infusion of the highest dose of LY293558 (60 mg/kg/24 h) was

ineffective in preventing the development of **analgesic** tolerance to DPDPE or U50488H. Continuous s.c. infusion of LY293558 (60 mg/kg/24 h) for 3 days protected mice from generalized convulsions produced by the selective AMPA agonist ATPA, indicating that the dosage of LY293558 that attenuated morphine tolerance was effective as an antagonist at AMPA receptors. These results demonstrate that AMPA receptors may play a role in the development and maintenance of morphine, but not DPDPE or U50488H, **analgesic** tolerance.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(competitive AMPA receptor antagonist LY293558 attenuation and reversal of **analgesic** tolerance to .mu. opioid but not to .delta. or .kappa. opioids)

L60 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:795591 HCAPLUS
DOCUMENT NUMBER: 128:123724
TITLE: The effects of LY293558, an AMPA receptor antagonist, on acute and chronic morphine dependence
AUTHOR(S): McLemore, Gabrielle L.; Kest, Benjamin; Inturrisi, Charles E.
CORPORATE SOURCE: York Avenue, LC-524, Department of Pharmacology, Cornell University Medical College, New York, NY 10021, 1300, USA
SOURCE: Brain Research (1997), 778(1), 120-126
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In rodents, noncompetitive and competitive NMDA receptor antagonists have been shown to attenuate and, in some cases, reverse tolerance to the **analgesic** effects of morphine. However, the ability of these same excitatory amino acid (EAA) receptor antagonists to modulate morphine dependence is controversial, and very little is known about the role of AMPA receptors in morphine dependence. LY293558, a novel, systemically active, competitive AMPA receptor antagonist and the NMDA receptor antagonists, MK-801 and/or LY235959, were evaluated in tolerant or dependent CD-1 mice. In mice rendered tolerant by morphine injection or pellet implantation, continuous s.c. infusion of LY293558 (60 mg/kg per 24 h) or MK-801 (1 mg/kg per 24 h) attenuated the development of tolerance. Neither LY293558 nor MK-801 produced **analgesia** or altered the ED50 value of morphine. Continuous s.c. infusion of LY293558 (60 mg/kg per 24 h), MK-801 (1 mg/kg per 24 h) or LY235959 (12 mg/kg per 24 h) attenuated the development of acute (3 h) morphine dependence (i.e., decreased naloxone-pptd. withdrawal jumping). In contrast, continuous s.c. infusion of LY293558 (60 mg/kg per 24 h) or LY235959 (12 mg/kg per 24 h) did not significantly attenuate the development of chronic dependence produced by morphine pellet implantation. These data indicate that the development of morphine tolerance is more sensitive to modulation by EAA receptor antagonists than is the development of morphine dependence as assessed by naloxone-pptd. withdrawal jumping.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of AMPA and NMDA receptor antagonists on acute and chronic morphine dependence)

L60 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:213193 HCAPLUS
DOCUMENT NUMBER: 126:288414
TITLE: L-trans-Pyrrolidine-2,4-dicarboxylic acid-evoked striatal glutamate levels are attenuated by calcium

reduction, tetrodotoxin, and glutamate receptor blockade
AUTHOR(S): Rawls, Scott M.; Mcginty, Jacqueline F.
CORPORATE SOURCE: Department of Anatomy and Cell Biology, East Carolina University School of Medicine, Greenville, NC, 27858-4354, USA
SOURCE: Journal of Neurochemistry (1997), 68(4), 1553-1563
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB L-trans-Pyrrolidine-2,4-dicarboxylic acid (L-trans-PDC) reverses plasma membrane glutamate transporters and elevates extracellular glutamate levels in vivo. We investigated the possibility that L-trans-PDC-stimulated glutamate levels are mediated partially by increases in transsynaptic activity. Therefore, the degree to which L-trans-PDC-evoked glutamate levels depend on calcium, sodium-channel activation, and glutamate-receptor activation was investigated by infusing via reverse microdialysis (a) 0.1 mM calcium, (b) 1 .mu.M tetrodotoxin, a selective blocker of voltage-dependent sodium channels, (c) R(-)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), a selective NMDA-receptor antagonist, or (d) LY293558, a selective .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionate antagonist. In sep. exptl. groups, L-trans-PDC-evoked glutamate levels were reduced significantly by 55% in the presence of 0.1 mM calcium and by 46% in the presence of tetrodotoxin. Addnl., CPP and LY293558 significantly attenuated L-trans-PDC-evoked glutamate levels without altering basal glutamate levels. These data suggest that glutamate transporter reversal by L-trans-PDC initially elevates extracellular glutamate levels enough to stimulate postsynaptic glutamate receptors within the striatum. It is proposed that glutamate-receptor stimulation activates a pos. feedback loop within the basal ganglia, leading to further glutamate release from corticostriatal and thalamostriatal afferents. Therefore, either extracellular striatal calcium redn. or tetrodotoxin perfusion leads to decreased action potential-dependent glutamate release from these terminals. In addn., blocking glutamate receptors directly reduces medium **spiny** neuronal firing and indirectly attenuates corticostriatal and thalamostriatal activity, resulting in an overall depression of L-trans-PDC-stimulated glutamate levels.
IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pyrrolidinedicarboxylate-evoked striatal glutamate levels are attenuated by calcium redn., tetrodotoxin, and glutamate receptor blockade)

L60 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:691762 HCAPLUS
DOCUMENT NUMBER: 126:181183
TITLE: A selective AMPA antagonist, LY293558, suppresses morphine withdrawal-induced activation of locus coeruleus neurons and behavioral signs of morphine withdrawal
AUTHOR(S): Rasmussen, Kurt; Kendrick, William T.; Kogan, Jeffrey H.; Aghajanian, George K.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Neuropsychopharmacology (1996), 15(5), 497-505
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The glutamate receptor subtype that mediates the morphine

withdrawal-induced activation of locus coeruleus (LC) neurons was examd. in this study using in vitro and in vivo single-unit electrophysiol. recordings. For LC neurons recorded in vitro in rat brain slices, the selective .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonist, LY293558, showed a greater than 10-fold selectivity for inhibiting the excitatory effects of AMPA vs. kainate, and a greater than 30-fold selectivity for inhibiting the excitatory effects of AMPA vs. NMDA. LY293558 also greatly reduced the response of LC neurons to glutamate in a concn.-dependent manner. In in vivo recordings in **anesthetized** rats, pretreatment with LY293558 (0.1 to 10 mg/kg, IP) dose dependently suppressed the morphine withdrawal-induced activation of LC neurons. In unanesthetized, morphine-dependent animals, pretreatment with LY293558 (1 to 30 mg/kg, IP) dose dependently suppressed naltrexone-pptd. morphine withdrawal signs. These results indicate: (1) AMPA receptors mediate a large component of the excitatory effects of glutamate on LC neurons; (2) activation of AMPA receptors plays an important role in the morphine withdrawal-induced activation of LC neurons; (3) AMPA antagonists can suppress many signs of morphine withdrawal in awake animals; and (4) AMPA antagonists may have therapeutic effects in humans for the treatment of opiate withdrawal.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AMPA antagonist LY293558 suppresses morphine withdrawal-induced activation of locus coeruleus neurons and behavioral signs of morphine withdrawal)

L60 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:586657 HCAPLUS
DOCUMENT NUMBER: 125:238444
TITLE: The AMPA antagonist LY293558 improves functional neurological outcome following reversible **spinal** cord ischemia in rabbits
AUTHOR(S): Bowes, Mark P.; Swanson, Steven; Zivin, Justin A.
CORPORATE SOURCE: School Medicine, University California, La Jolla, CA, 92093-0624, USA
SOURCE: Journal of Cerebral Blood Flow and Metabolism (1996), 16(5), 967-972
CODEN: JCBMDN; ISSN: 0271-678X
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamate (Glu) neurotoxicity is an important element of a no. of neurol. disorders including central nervous system (CNS) ischemia. We evaluated the effects of the novel AMPA Glu antagonist LY293558 on functional neurol. outcome in two rabbit stroke models. In the reversible **spinal** cord ischemia model, ischemia of the caudal lumbar **spinal** cord was produced by temporary occlusion of the abdominal aorta. LY293558 was administered 5 min after recirculation as a 16 mg/kg i.v. bolus followed by 2.2 mg/kg infused over 1 h. Control animals received saline. LY293558 significantly increased the duration of ischemia required to produce paraplegia, from 30.5 .+-. 15.8 min (mean .+-. SD) controls to 50.1 .+-. 11.5 in treated animals ($p < 0.01$). In an irreversible model of cerebral ischemia, 50 .mu.m plastic microspheres were injected into the carotid artery and lodged in the cerebral microvasculature. LY293558 did not significantly reduce neurol. damage in this model. These data suggest that LY293558 may have therapeutic benefit following some types of ischemic injury.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(AMPA antagonist LY293558 improves functional neurol. outcome following reversible **spinal** cord ischemia)

L60 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:525011 HCAPLUS
DOCUMENT NUMBER: 121:125011
TITLE: Neuroprotective effect of the AMPA receptor antagonist LY-293558 in focal cerebral ischemia in the cat
AUTHOR(S): Bullock, R.; Graham, D. I.; Swanson, S.; McCulloch, J.
CORPORATE SOURCE: Wellcome Surg. Inst. and Hugh Fraser Neurosci. Lab., Univ. Glasgow, Glasgow/Scotland, G61 1QH, UK
SOURCE: Journal of Cerebral Blood Flow and Metabolism (1994), 14(3), 466-71
CODEN: JCBMDN; ISSN: 0271-678X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the glutamate .alpha.-amino-3-hydroxy 5-methyl-4-isoxazole propionate (AMPA) receptor antagonist LY-293558 in reducing ischemic brain damage have been assessed in halothane-**anesthetized** cats. Focal cerebral ischemia was produced by permanent occlusion of one middle cerebral artery, and the animals were killed 6 h later. The amt. of early irreversible ischemic damage was assessed at 16 predetd. stereotactic planes by an observer blinded to treatment paradigm employed. Treatment with LY-293558 (15 mg/kg i.v., plus infusion of 7 mg/kg/h) initiated 30 min prior to middle cerebral artery occlusion reduced significantly ($p < 0.02$) the vol. of ischemic damage (from 3,423 .+-. 212 mm3 of the cerebral hemisphere in vehicle-treated cats to 2,822 .+-. 569 mm3 in LY-293558-treated cats). The present data demonstrate that an AMPA receptor antagonist can reduce focal ischemic damage in a gyrencephalic species in which key physiol. variables have been controlled and monitored throughout the postischemic period. These data provide addnl. support for the clin. evaluation of AMPA receptor antagonists in focal cerebral ischemia in humans.

IT **154652-83-2**, LY-293558
RL: PRP (Properties)
(neuroprotective effect of, in focal cerebral ischemia)